PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
C 2481 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/00598	26/01/2000	27/01/1999
International Patent Classification (IPC) or national classification and IPC		
A61K9/127		
Applicant		
IDEA AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 14 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28/07/2000	23.04.2001
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I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-63	as originally filed				

Claims, No.:

1-52	as received on	08/03/2001	with letter of	08/03/2001	

Drawings, sheets:

1/24-24/24	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 2, 4-52.

because:

☒ the said international application, or the said claims Nos. 45-52 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 2, 4-52 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims

	No:	Claims	1,3
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,3
Industrial applicability (IA)	Yes:	Claims	1,3
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The subject-matter of claim 2 lacks clarity. Claim 2 relates to the "use of a penetrant", wherein the use is not clearly defined. It is unclear from the wording of the said claim as to whether the use of a penetrant is claimed or the use of a combination of penetrant and an active substance for the preparation of a transnasally administrable pharmaceutical composition. Moreover, it is unclear as whether a "second-medical use" is intended related to the use for the treatment of some specific diseases. Finally, it is also unclear whether the last sentence "and/or for use in the field of ...." relates to the medical use of the combination comprising the penetrant or is given as an alternative definition for the active substance.

3. Claims 4-42 lack clarity since their wording includes simmultaneously two categories (product and use) as alternatives. Therefore, the scope for which protection is sought by the said claims remains so unclear that no opinion on novelty and inventive step can be given of the subject-matter claimed therein.

   Claim 45 relates to a "method for generating a protective immuno response on a mammal by vaccinating the mammal with a vaccine according to one of claims 35-42". This multiple reference renders the scope of claim 45 unclear since the mentioned claims are not equivalent alternatives. The same applies to dependent claims 46-52.

   An analogous analysis applies to the subject-matter of claims 43 and 44, insofar as the pharmaceutical composition is defined as one of claims 4-42.

4. The Applicant is reminded of the fact that the **claims** define the subject-matter for which protection is sought (Article 6 PCT). Therefore the obscure and vague wording employed in the above mentioned claims for defining the subject-matter for which protection is sought does not allow the examiner to assess on their novelty and inventive step.

5. Claims 45-52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents have been considered for the establishment of the present preliminary examination report:

   D1 = EP 0 475 160 A
   D2 = WO 9817255 A (cited in the application)
   D3 = DE 4107152 A (cited in the application)
   D4 = DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US ALMEIDA A J ET AL: "Nasal delivery of vaccines." XP002107393 -& JOURNAL OF DRUG TARGETING, (1996) 3 (6) 455-67. REF: 125 JOURNAL CODE: B3S. ISSN: 1061-186X., XP002109107 Switzerland
   D5= WO 90 09385 A

2. The penetrant in the form of a minute fluid droplet and its use for the preparation of a pharmaceutical as defined in claim 1, and the pharmaceutical composition comprising the said penetrant as carrier as defined in claim 3, are known in the art (cf. D1 to D3). The expression "preferably a vaccine composition for transnasal administration" employed in claim 1 has no limitative character. Therefore the subject-matter claimed in claims 1 and 3 lacks novelty. On page 13 of the description of the present application it has been acknowledged that the penetrants according to the present application are known as carriers in pharmaceutical formulations. Most of the characterizing features given in the said claims are either optional or relate to results-to-be-achieved and hence cannot be taken as clear technical features for defining the contribution to the art.

3. The problem underlying the present application appears to lie in the preparation of pharmaceutical fomulation useful for the transnasal administration of active substances, antigens or allergens.

D1 to D3 discloses the use of the penetrants such as those of the present application as carriers for the non-invasive administration of active substances (eg. insuline), especially transdermal.

D4 shows the general teaching relating to the nasal delivery of vaccines. D4 demonstrates that generally known carriers systems such as liposomes, microparticles and nanoparticles may be employed with expectation of success for the transnasal administration. This is also shown by D5 which discloses lipid excipients useful for both nasal delivery and topic application.

Therefore the subject-matter claimed in the present claims 1 and 3 does not involve an inventive step.

4. For the assessment of the present claims 1, 3 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

1. Use of a penetrant, suspended or dispersed in a solvent, in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances or two different forms of a substance with the tendency to aggregate, said substances or forms of a substance differing by at least the factor of 10 in the solubility in a preferably aqueous, liquid medium, such that the average diameter of homo-aggregates of the more soluble substance or form of the substance or the average diameter of the hetero-aggregates consisting of both said substances or forms of said substance is smaller than the average diameter of homo-aggregates of the less soluble substance or forms of the substance and/or wherein the more soluble component tends to solubilise the penetrating droplet and wherein the content of such component amounts to up to 99 mol-% of the concentration required to solubilise the droplet or else corresponds to up to 99 mol-% of the saturating concentration in the un-solubilised droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounding the membrane-like coating is at least 5x lower, more preferably is at least 10x lower and ideally is more than 10x lower than that of the red blood cells or of the phospholipid bilayers with fluid aliphatic chains as a carrier for the preparation of a pharmaceutical, preferably a vaccine composition for transnasal administration.

2. Use of a penetrant, suspended or dispersed in a solvent, in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances or two different forms of a substance with the tendency to aggregate, said substances or forms of a substance differing by at least the factor of 10 in the solubility in a preferably

aqueous, liquid medium, such that the average diameter of homo-aggregates of the more soluble substance or form of the substance or the average diameter of the hetero-aggregates consisting of both said substances or forms of said substance is smaller than the average diameter of homo-aggregates of the less soluble substance or form of the substance and/or wherein the more soluble component tends to solubilise the penetrating droplet and wherein the content of such component amounts to up to 99 mol-% of the concentration required to solubilise the droplet or else corresponds to up to 99 mol-% of the saturating concentration in the un-solubilised droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounding the membrane-like coating is at least 5x lower, more preferably is at least 10x lower and ideally is more than 10x lower than that of the red blood cells or of the phospholipid bilayers with fluid aliphatic chains, said penetrant being used in combination with a pharmaceutically active ingredient or an allergen or an antigen for the preparation of a transnasally administerable pharmaceutical composition for the treatment of infective diseases, endocrine disorders, preferably hypopituitarism, diabetes, hyperthyroidism, thyroiditis, most preferably Hashimoto's thyroiditis, subacute thyroiditis; adrenal disorders, preferably Addison's disease, secondary adrenal insufficiency, Cushing's syndrome; gastrointestinal disorders, preferably Crohn's disease, colitis; hemorrhagic diseases, preferably hemophilia, leukopenia, hypereosinophilic syndrome; musculoskeletal and connective tissue disorders, preferably rheumatoid arthritis, Sjögren's syndrome, Bechet's syndrome, lupus, scleroderma, polymyositis/dermatomyositis, polymyalgia rheumatica and temporal arthritis, polyarteriosis nodosa, Wegener's granulomatosis, mixed connective tissue disorder, ankylosing spondylitis, psoriatic arthritis, osteoarthritis, Paget's disease, sciatica, bursitis, tendonitis and tenosynovitis, epicondylitis, fibromyalgia, eosinophilic faciitis; neurological disorders, preferably pain, singultus, vertigo, seizure disorders, sleep disorders, transient ischemic attacks, spinal cord injury, demyelinating diseases, nerve root disorders, myasthenia gravis; oncological disorders; psychiatric disorders, preferably drug dependence, neuroses, mood disorders, schizophrenic disorders,

delusional disorders; and/or for use in the field of gynecology, preferably for the treatment of dysmenorrhea, menopause, chronic anovulation, premature ovarian failure, endometriosis, infertility; and/or for use in the field of immunology, preferably transplant rejection, hyposensitation, allergen immunotherapy or prophylactic vaccination.

3. A pharmaceutical composition for transnasal administration comprising a carrier, which is a penetrant, suspended or dispersed in an aqueous solvent, in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances or two different forms of a substance with the tendency to aggregate, said substances or forms of a substance differing by at least the factor of 10 in solubility in a preferably aqueous, liquid medium, such that the average diameter of homo-aggregates of the more soluble substance or form of the substance or the average diameter of the hetero-aggregates consisting of both said substances or forms of said substance is smaller than the average diameter of homo-aggregates of the less soluble substance or form of the substance and/or wherein the more soluble component tends to solubilise the penetrating droplet and wherein the content of such component amounts to up to 99 mol-% of the concentration required to solubilise the droplet or else corresponds to up to 99 mol-% of the saturating concentration in the un-solubilised droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounding the membrane-like coating is at least 5x lower, more preferably is at least 10x lower and ideally is more than 10x lower than that of the red blood cells or of the phospholipid bilayers with fluid aliphatic chains said composition also including a pharmaceutically active ingredient, an allergen, an antigen, a mixture of antigens and/or a mixture of allergens.

4. The use of claim 2 or the pharmaceutical composition of claim 3 wherein the pharmaceutically active ingredient is an adrenocorticostaticum, an adrenolyticum, an androgen or antiandrogen, an antiparasiticum, an anabolicum, an anaestheticum or analgesicum, an analepticum, an

antiallergicum, antiarrhythmicum, antiarteroscleroticum, antiasthmaticum and/or bronchospasmolyticum, an antibioticum, an anti-infective agent, antidepressivum and/or antipsychoticum, an antidiabeticum, an antidot, an antiemeticum, antiepilepticum, antifibrinolyticum, anticonvulsivum or anticholinergicum, an enzyme, a coenzyme or the corresponding enzyme inhibitor, an antihistaminicum (and combinations thereof) or antihypertonicum, an antihypotonicum, anticoagulant, antimycoticum, antimyasthenicum, an agent against Morbus Alzheimer or Morbus Parkinson, an agent for ACS therapy, an antiphlogisticum, antipyreticum, antirheumaticum, antisepticum, a respiratory analepticum or a respiratory stimulant, a broncholyticum, cardiotonicum, chemotherapeuticum, a coronary dilatator, a cytostaticum, a diureticum, a ganglium-blocker, a glucocorticoid, an anti-flew agent, a haemostaticum, hypnoticum, an immunoglobuline or its fragment or any other immunologically active substance, such as an immunomodulator, a bioactive carbohydrate (derivative), a contraceptive, an anti-migraine agent, a corticosteroid, a muscle relaxant, a narcoticum, a neurotherapeuticum, a (poly)nucleotide, a neurolepticum, a neurotransmitter, a (poly)peptide (derivative), an opiate, an opthalmicum, (para)-sympaticomimeticum or (para)sympathicolyticum, a protein(derivative), a psoriasis/neurodermitis drug, a mydriaticum, a psychostimulant, rhinologicum, a sleep-inducing agent, a sedating agent, a spasmolyticum, tuberculostaticum, urologicum, a vasoconstrictor or vasodilatator, a virustaticum, a wound-healing substance, an alcohol abuse preparation, an anticonvulsant, an antineoplastic, an antirheumatic, an appetite suppressant, a biological response modifier, a blood modifier, a bone metabolism regulator, a cardioprotective agent, a cardiovascular agent, a central nervous system stimulant, an enzyme, an agent for erectile dysfunction therapy, a fertility agent, a gastrointestinal agent, a gout preparation, a hormone, an agent for hypercalcemia management, an agent for hypocalcemia management, an immunosuppressive, a migraine preparation, a motion sickness product, an agent for multiple sclerosis management, a muscle relaxant, a nutritional, an ophthalmic preparation, an osteoporosis preparation, an otic preparation, a parasympatholytic, a parasympathomimetic, a prostaglandin, a

psychotherapeutic agent, a respiratory agent, a sedative & hyponotic, a skin & muccus membrane agent, a smoking cessation aid, a sympatholytic, a tremor preparation, a urinary tract agent, a vaginal preparation, a vertigo agent, an immunologically active substance (such as an immunomodulator, e.g., bacterial extracts or cell wall components like cholera toxin, heat labile toxin, monophosphoryllipid A, or cytokine inducing agents or hormones like thymosin, thymulin, thymopoietin, or phytoimmunostimulants like extracts from Echinacea root, wild indigo root, white cedar leave tips, or synthetic immunomodulators like quinoline derivatives, synthetic peptides, pyrimidine, lipopeptides, or cytokines or immunosuppressants, and signal transduction inhibitors like cyclosporin A, FK506, FTY720, rapamycin), an inhibitor (antagonist), or a promotor (agonist) of the activity of any of above mentioned agents, or any combination of said active substances.

5. The use of claim 2 or the pharmaceutical composition of claim 3 wherein the antigen is derived from a pathogen.

6. The use of claim 2 or the pharmaceutical composition of claim 3 wherein said pathogen belongs to extracellular bacteria, including pus-forming cocci, such as *Staphylococcus* and *Streptococcus*, gram-negative bacteria, such as Meningococcus and Gonococcus species, species of *Neisseria,* gram negative bacteria, including enteric organisms such as *E. coli, Salmonella, Shigella, Pseudomonas, Diptheria, Bordetella Pertussis,* and gram-positive bacteria (e.g. *Bacillus pestis, BCG*), particularly anaerobes, such as the *Clostridium* species (e.g. *Clostridium tetani, Clostridium perfringens, Clostridium novyi, Clostridium septicum*), bacteria and viruses, which survive and replicate within host cells, comprising mycobacteria (e.g. *M. tuberculosis*) and *Listeria monocytogenes*, retro- and adenoviruses, including hepatitis virus, (human) immunodeficiency virus, herpex viruses, small-pox (chicken-pox), influenza, measles, mumps and polio viruses, cytomegalovirus, rhinovirus, etc., and fungi prospering inside host cells, a parasite including animal parasites, such as protozoa and helminths, and ectoparasites, such as ticks and mites, or *Brucella* species, (e.g. B. melitensis, B. abortus, B.

suis, B. canis, B. neotomae, B. ovis, the causative agent for cholera (e.g. Vibrio cholerae), *Haemophilus* species like H. actinomycentemcomitans, H. pleuropneumoniae , as well as pathogens triggering paratyphoid, plague, rabies, tetanus and rubella diseases or to eukaryotic cells or their parts that cause various neoplasiae, auto-immune diseases and other pathological states of the animal or human body which do not necessarily result from microbial infections.

7. The use of claim 2 or the pharmaceutical composition of claim 3 wherein the antigen is used in a purified or even better in a pure form.

8. The use of claim 2 or the pharmaceutical composition of claim 3 wherein the antigen is the antigenic determinant of hepatitis virus, (human) immunodeficiency virus, herpex viruses, small-pox (chicken-pox), influenza, measles, mumps and polio viruses, cytomegalovirus, rhinovirus, etc., and fungi prospering inside host cells, a parasite including animal parasites, such as protozoa and helminths, and ectoparasites, such as ticks and mites, or *Brucella* species, including the causative agent for cholera, Haemophilus species, as well as pathogens triggering paratyphoid, plague, rabies, tetanus and rubella diseases or else eukaryotic cells or their parts that cause various neoplasiae, auto-immune diseases and other pathological states of the animal or human body, which do not necessarily result from microbial infections.

9. The use of claim 2 or the pharmaceutical composition of claim 3, wherein the allergen is of xenogenic or endogenic origin, derived from a microorganism, an animal or a plant, or belonging to the group of man made and/or irritating inorganic substances, or to such parts or components of the human body which were incorrectly processed by or exposed to the body immune system.

10. The use of claim 2 or the pharmaceutical composition of claim 3 wherein the allergen belongs to the class of the inhalation allergens, including but not limited to various pollen, spores, bits of animal hair, skin, feather, natural and

synthetic textiles, wheat, (house) dust, including mite; furthermore, food and drug allergens; contact allergens; injection, invasion or depot allergens, such as various (gastrointestine-resident) worms, echinococci, trichines, etc., a part of implantation material.

11. The use of any one of claims 1 to 2 and 4 to 10 or the pharmaceutical composition of any one of claims 3 to 8 additionally comprising a compound which releases or induces cytokine or anti-cytokine activity or exerts such an activity itself.

12. The use or the pharmaceutical composition of claim 11 wherein the compound exerting cytokine activity is IL-4, IL-3, IL-2, TGF, IL-6, TNF, IL-1α and/or IL-1β, a type I interferon, preferably IFN-alpha or IFN-β, IL-12, IFN-γ, TNF-β, IL-5 or IL-10.

13. The use or the pharmaceutical composition of claim 11 wherein said compound with anti-cytokine activity is an anti-cytokine antibody or the corresponding active fragment, a derivative, or an analogue thereof.

14. The use or the pharmaceutical composition of claim 3 wherein the compound displaying or inducing cytokine or anti-cytokine activity and the pharmaceutically active ingredient or antigen or allergen are associated with the penetrant.

15. The use of any one of claims 1 to 14 or the pharmaceutical composition of any one of claims 3 to 14 wherein the less soluble self-aggregating molecule is a lipid, preferably a polar lipid, and the more soluble component is a surfactant or some more soluble form of the polar/basic lipid.

16. The use of any one of claims 1 to 15 or the pharmaceutical composition of any one of claims 3 to 15 wherein the more soluble component is an agent to be transported across the barrier, said agent having a tendency to form

common large structures with the less soluble component(s) of the penetrant, typically in the form of a physical or a chemical complex.

17. The use of any one of claims 1 to 16 or the pharmaceutical composition of any one of claims 3 to 16 wherein the more soluble component tends to solubilise the penetrating droplet and is present in concentration not exceeding 99 mol% of the concentration required to disintegrate the droplet or, alternatively, not exceeding 99 mol% of the saturating concentration in the unsolubilised droplet, whichever is higher, values below 50% of the former relative concentration being particularly useful, with values below 40 rel-% or even around and below 30 rel-% being even more advantageous, whereas in the case of droplets which cannot be solubilised by the more soluble component relative concentrations which exceed the above mentioned relative concentrations by the factor of up to 2 are most preferred.

18. The use of any one of claims 1 to 17 or the pharmaceutical composition of any one of claims 3 to 17 wherein the less soluble penetrant component is a polar lipid and the more soluble component is a surfactant or a surfactant-like molecule or else such form of a lipid, preferably a polar lipid which is sufficiently soluble for the purpose of this invention.

19. The use of any one of claims 1 to 18 or the pharmaceutical composition of any one of claims 3 to 18 wherein the average penetrant diameter is between 25 nm and 500 nm, preferably between 30 nm and 250 nm, even more preferably between 35 nm and 200 nm and particularly preferably between 40 nm and 150 nm.

20. The use of any one of claims 1 to 19 or the pharmaceutical composition of any one of claims 3 to 19 wherein the penetrant concentration in the formulation for the use in human or animal nose is 0.001 to 20 weight-% of total dry mass in the formulation, in particular between 0.01 w-% and 15 w-%, more preferably between 0.1 w-% and 12.5 w-% and most preferred between 0.5 w-% and 10 w-%.

21. The use of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 3 to 20 wherein the supporting medium, e.g. a buffer, is selected to be a biocompatible solution with an osmotic activity similar to that of a monovalent electrolyte with concentration in the range between 1 mM and 500 mM, more preferably between 10 mM and 400 mM, even more preferably between 50 mM and 300 mM, and most preferably between 100 mM and 200 mM or else such solution that affords practically sufficient penetrant stability combined with practically sufficient transport rate across the barrier.

22. The use of any one of claims 1 to 21 or the pharmaceutical composition of any one of claims 3 to 21 wherein the relative drug or agent concentration is between 0.001 and 40 weight-% of total penetrant mass, in particular between 0.01 w-% and 30 w-%, even better between 0.1 w-% and 25 w-% and most preferably between 0.5 w-% and 15 w-%.

23. The use of any one of claims 1 to 22 or the pharmaceutical composition of any one of claims 3 to 22 wherein the medium supporting the drugs and carriers is a biocompatible buffer with pH value between 4 and 10, more frequently between 5 and 9 and most often between 6 and 8.

24. The use of any one of claims 1 to 23 or the pharmaceutical composition of any one of claims 3 to 23 wherein the additives are included in the preparation to reduce the system sensitivity to chemical, biological or ambient stress, including anti-oxidants, antagonists of undesired enzyme action, cryo-preservants, microbicides, etc., or else modulators of physically important system properties, such as formulation viscosity, etc..

25. The use of any one of claims 1 to 24 or the pharmaceutical composition of any one of claims 3 to 24 wherein the relative drug or agent dose to be administered non-invasively through the nose by means of highly adaptable carriers is chosen to be between 0.1x and 500x, more often between 0.5x and

250x, and even more preferably between 1x and 100x different from the corresponding drug or agent dose that would have to be injected to achieve the desired biological effects.

26. The use of any one of claims 1 to 25 or the pharmaceutical composition of any one of claims 3 to 25 wherein the applied penetrant dose is between 0.01 mg and 15 mg per nostril, even more often is in the range 0.1 mg and 10 mg per nostril, and preferably is between 0.5 mg and 5 mg per nostril.

27. The use of any one of claims 1 to 26 or the pharmaceutical composition of any one of claims 3 to 26 wherein the efficiency of administration and the biological effects of the agent or drug chosen are controlled by using different application volumes.

28. The use of any one of claims 1 to 27 or the pharmaceutical composition of any one of claims 3 to 27 wherein said formulation is administered using a metered delivery device.

29. The use of any one of claims 1 to 28 or the pharmaceutical composition of any one of claims 3 to 28 wherein different application volumes are selected to control the efficiency of administration and the biological effects of the chosen agent or drug.

30. The use of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 3 to 29 wherein the penetrants in suspension are loaded with the drugs or agents within 24 hours prior to the formulation administration, preferably 360 min, more preferably 60 min and even more preferably 30 min before the resulting formulation administration in the nose.

31. The use of any one of claims 1 to 30 or the pharmaceutical composition of any one of claims 3 to 30 wherein the delivery device is loaded at the treatment site.

32. The use of any one of claims 1 to 31 or the pharmaceutical composition of any one of claims 3 to 31 wherein the device is loaded separately with penetrants and the molecules, particularly biological agents, to be associated therewith.

33. The use of any one of claims 1 to 32 or the pharmaceutical composition of any one of claims 3 to 32 wherein the pharmaceutically active ingredient is for administration to the nervous system.

34. The use or the pharmaceutical composition of claim 33 wherein the nervous system is the brain.

35. The use of any one of claims 1 to 34 or the pharmaceutical composition according to any one of claims 3 to 34 wherein said pharmaceutical composition is a vaccine.

36. The vaccine of claim 35 which further comprises a pathogen extract or a compound from a pathogen or a fragment or a derivative thereof.

37. The vaccine of claim 36 wherein said pathogen extract or compound is selected from hepatitis virus, (human) immunodeficiency virus, herpex viruses, small-pox (chicken-pox), influenza, measles, mumps or polio viruses, cytomegalovirus, rhinovirus, etc., or fungi prospering inside host cells, a parasite including animal parasites, such as protozoa and helminths, and ectoparasites, such as ticks and mites, or *Brucella* species, including the causative agent for cholera, Haemophilus species, as well as pathogens triggering paratyphoid, plague, rabies, tetanus or rubella diseases.

38. The vaccine of any one of claims 35 to 37 which further comprises an adjuvant.

39. The vaccine of claim 37 or 38 wherein said adjuvant is lipopolysaccharide, such as lipid A or a derivative or modification thereof, such as

monophosphoryl lipid A, or its analogue, such as a fatty derivative of saccharose, cord-factor (trehalose-dimycolate), muramyl dipeptide, or another (poly)saccharide or (poly)peptide identical to or resembling an immunologically active part of a membrane of a microorganism; an extract of a microorganism, including bacterial exo- and endotoxins, preferably cholera toxin or the heat labile toxin of *E. coli*, an A-chain derivative, a component with an ADP-ribosylating activity, a peptidoglycane, a clostridial toxin, an LT halotoxin, purified protein derivative of *M. tuberculosis*, LT-R192G, Fibronectin-binding protein I of *Streptococcus pyrogenes*, or outer membrane protein of group B *Neisseria meningitidis* (GBOMP), bacterial or viral nucleic acids, such as oligonucleotides comprising unmethylated CpG dinucleotides.

40. The vaccine of any one of claims 35 to 39 comprising a blend of MPL and IL-12 or GM-CSF and IL-4.

41. The vaccine of any one of claims 35 to 40 wherein the relative immunogen/antigen dose to be administered non-invasively through the nose by means of highly adaptable carriers is chosen to be between 0.01x and 100x, more often between 0.05x and 75x, and even more preferably between 0.1x and 50x different from the corresponding immunogen/antigen dose that would have to be injected to achieve the desired biological effect.

42. The vaccine according to any one of claims 38 to 41 wherein the concentration of the transnasally administered adjuvant is between 10x lower and up to 1000x higher than that used with the corresponding subcutaneously injected formulations employing similar antigen, the transnasally administered immunoadjuvant concentration more often differing from the injected immunoadjuvant concentration by the factor between 0.5 and 100, or better, by the factor between 1 and 50, and best between 2 and 25.

43. A container comprising the pharmaceutical composition according to any one of claims 3 to 42.

Amended claims

44. A package comprising at least one container comprising the pharmaceutical composition of any one of claims 3 to 42.

45. A method for generating a protective immuno response on a mammal by vaccinating said mammal with a vaccine according to any one of claims 35 to 42.

46. The method according to claim 45 wherein different administration volumes are selected to control the applied immunogen dose and the outcome of vaccination.

47. The method according to claim 45 or 46, wherein a suspension of antigen-free penetrants is loaded with the antigen to be associated therewith during the day prior to an administration, preferably 360 min, more preferably 60 min and even more preferably 30 min before administering the resulting formulation in the nose.

48. The method of any one of claims 45 to 47 characterised in that at least one dose of vaccine is administered.

49. The method according to claim 48 wherein said vaccine is administered as a booster vaccination.

50. The method according to any one of claims 45 to 49, wherein the vaccine is applied between 2 and 10, preferably between 2 and 7, even more preferably up to 5 and most preferably up to 3 times, when a non-allergenic antigen is used, or such a number of times, in the case of allergens, as is required either to achieve the desired immuno-tolerance, determined according to a suitable assessment method, or else to deem the effort as having failed.

51. The method according to any one of claims 47 to 50, wherein the time interval between the subsequent vaccinations is chosen to be between 2 weeks and 5 years, often between 1 month and up to 3 years, more

frequently between 2 months and 1.5 years.

52. The method according to any one of claims 45 to 51, wherein the flux of penetrants that carry an immunogen through the various pores in a well-defined barrier is determined as a function of a suitable driving force or a pressure acting across the barrier and the data are then conveniently described by a characteristic curve which, in turn, is employed to optimise the formulation or application further.